Three-Center CF···HN Intramolecular Hydrogen Bonding in the 2,6-Bis(2,6-difluorophenyl)piperidine Systems[1]

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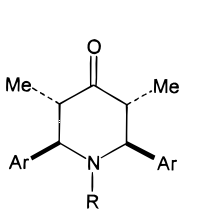
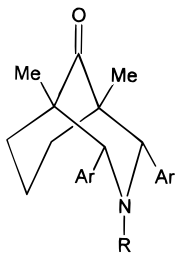
^{1}H, ^{13}C, and ^{19}F NMR spectroscopy provided evidence for an interaction between the NH proton and the neighboring fluorine atoms in 2,6-bis(2,6-difluorophenyl)piperidin-4-ones, which can be qualified as a three-center hydrogen bonding. This was confirmed by the X-ray crystal structures of two compounds revealing the axial orientation of the amino hydrogen and its short contacts to two fluorine atoms. Surprisingly, the IR spectra exhibited shift of the NH stretching frequency to higher instead to lower wavenumbers in the 2,6-difluorophenyl derivatives. The variable temperature ^{19}F NMR spectra showed enhanced C−C rotation barriers of the aryl substituents in the 2,6-difluorophenyl derivatives, due to the intramolecular hydrogen bonding.

Intermolecular and intramolecular hydrogen bonds involving fluorine atom have been recently a subject of considerable interest.[2−6] It is related to importance of C−F bonds in some bioorganic systems,[3,5,7] for example, fluorinated enzyme substrate analogues, in which the fluorine atom replaces the isosteric hydroxyl oxygen. However, it has been recognized that the fluorine atom covalently linked to carbon is generally a much weaker hydrogen bonding acceptor than the oxygen or nitrogen atoms. Recent *ab initio* calculations performed by Howard et al.[2] and Dunitz and Taylor[3] have estimated the energy of the C−F···H−O interaction to be less than one-half of the strength of a hydrogen bond between oxygen and acidic hydrogen. Therefore, the search of the crystal structures deposited in the Cambridge Structural Database (CSD), carried out by the above authors and others,[2−5] have shown that short contacts between the covalently bound fluorine and the hydrogens of the OH and NH groups are extremely rare. The low proton affinity and thus unusually weak hydrogen bonding capability of the fluorine is due to its low basicity, low-lying 2p orbitals, and tightness of its electron shell.[3] In contrast, the fluorine atom in molecules of anionic character, like BF_4^-, SiF_6^{2-} and particularly the fluoride ion itself, is a strong proton acceptor.[8]

Hydrogen bonds usually involve one donor and one acceptor (two-center), though three-center (bifurcated) and four-center (trifurcated) hydrogen bondings are also known.[9] Three-center hydrogen bonds involving two oxygen atoms are relatively common in organic crystal structures,[10] whereas evidence for those involving two fluorine atoms bound to sp^2 or sp^3 hybridized carbons, to the best of our knowledge, has not been reported yet. Inspection of the NMR data of some 2,6-bis(2,6-difluorophenyl)piperidine derivatives, that have been prepared during our stereochemical studies on the 2,6-diarylpiperidine systems,[11] indicated existence of a three-center hydrogen bond between two fluorine atoms and the NH hydrogen in these compounds. In this paper we present spectroscopic and crystallographic evidence of this unusual example of intramolecular hydrogen bond in the above molecules. We also attempted to estimate a strength of this bond by the variable temperature ^{19}F NMR measurements.





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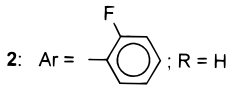
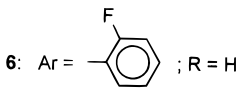
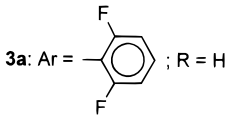
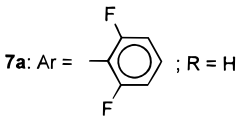
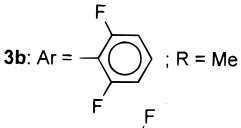
5: Ar = Ph; R = H

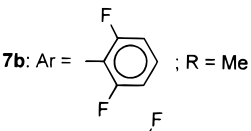


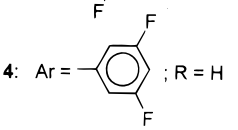


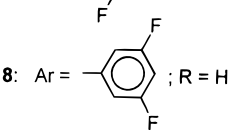












Results and Discussion

The amines **1**-**8** were obtained by a Mannich condensation of substituted benzaldehydes with appropriate ke-

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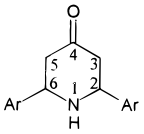
Table 1. Selected ^1H, ^{13}C and ^{19}F Chemical Shifts (δ in ppm) Measured in $CDCl_3$

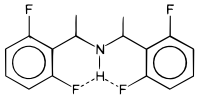


compd	NH	H(2), H(6)	C(2), C(6)	F
1	1.95	3.62	68.8	–
2	1.77	4.13	60.5	−119.1
3a	3.35	4.22[a]	58.8	−113.6, −114.2
3b	–	3.62	66.4	−109.6, −114.0
4	2.12	3.60	67.8	−106.8
5	1.86	3.94	71.5	–
6	1.55	4.45	62.0	−115.5
7a	4.33[b]	4.46[c]	62.6[d]	−109.7, −111.7
7b	–	3.78	70.9	−106.5, −109.2
8	1.72	3.94	70.3	−109.9

[a] $^3J_{CHNH} = 9.2$ Hz measured in the C_6D_6 solution. [b] $^5J_{HF} = 4.9$ Hz measured in the C_6D_6 solution. [c] $^3J_{CHNH} = 12.8$ Hz. [d] $^5J_{CF} = 2.7$ Hz.

tones and ammonium acetate according to the literature methods.[11,12]

The single-crystal X-ray and neutron diffraction, NMR, and IR spectroscopy are the most important experimental methods used for the detection of hydrogen bonding. Though there are some discussions on limitations and reliability of the NMR spectroscopy in this respect,[6,13] in our opinion this method gave an unequivocal indication of the interaction between the NH proton and the neighboring fluorine atoms in the amines **3a** and **7a**. The ^1H NMR spectra of 2,6-difluorophenyl compounds **3a** and **7a**, taken in the $CDCl_3$ solution, revealed the NH signals at an unusually low field (i.e., at 3.35 and 4.33 ppm, respectively) in contrast to the remaining amines showing the NH resonances in the range of 1.7−2.1 ppm (Table 1). Additionally, the NH proton in **7a** exhibits a long-range spin−spin coupling to two neighboring fluorine atoms ($^5J_{HF} = 4.9$ Hz). Unfortunately, severe line broadening of the NH signal in the spectrum of **3a** makes the measurement of $^5J_{HF}$ impossible for this compound. The observed downfield shift of the NH resonances and long-range coupling are consistent with the postulated symmetrical intramolecular three-center hydrogen bonding between the amino hydrogen and two neighboring fluorine atoms of two 2,6-difluorophenyl moieties, as shown below.



However, there might be a question if this coupling is transmitted via the hydrogen bonding or results only from a spatial proximity between the corresponding atoms, since a number of the long-range $^{19}F-^1H$ "through-space" interactions have been reported during the last several years.[14] On the other hand, it has been recently evidenced that the analogous couplings involving the fluorine atom in 2-fluorobenzamides are due to the C−F···H−N hydrogen bonding.[15] The above amides have also shown the spin−spin coupling of the aromatic fluorine to the carbonyl carbon, which is absent in the ^{13}C NMR spectrum of the corresponding *N*,*N*-dimethylamide. Similarly in our case, the ^{13}C NMR exhibited the C-2 and C-4 benzylic carbon signal in **7a** being split to a doublet, due to a coupling to only one aromatic fluorine atom ($^5J_{CF} = 2.7$ Hz). This coupling disappears in the *N*-methyl derivative **7b**. Apparently the six-membered ring formed by intramolecular hydrogen bonding in **7a** makes possible the coupling by the so-called "dual-path" mechanism.[16]

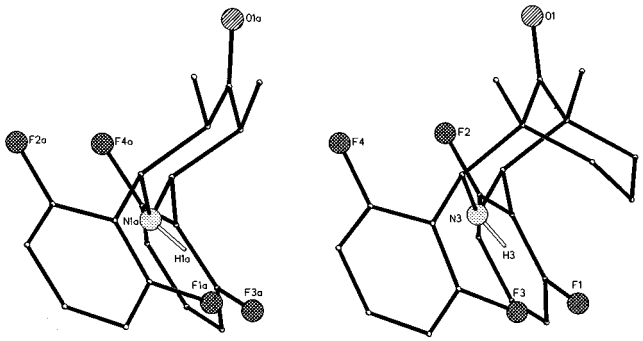


Figure 1. The crystal structures of **3a** (left) and **7a** (right).

The six-membered ring in *cis*-2,6-diarylpiperidin-4-ones prefers in solution as well as in the solid state a chair geometry with bulky substituents occupying equatorial positions, as known from the NMR and the X-ray crystallographic data.[17] Analogously, the bicyclic skeleton in *cis*-2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones adopts a twin-chair conformation, that is stabilized by equatorial aryl substituents.[11,18] The X-ray crystal structures of **3a** and **7a** are shown on Figure 1. There are two independent molecules of similar geometry in the asymmetric unit-cell of **3a**. The NH hydrogens can be easily localized at the axial positions in the crystals of both compounds from the difference electron density maps. The crystal structure of **3a** was determined at 100 K to get more reliable hydrogen atom localization, since at the room temperature a high percentage of measured reflections was unobserved. No residual electron density

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Table 2. Geometry of the Three-Center Intramolecular N−H···F Hydrogen Bonds

N−H···F	N···F (Å)	N−H (Å)	H···F (Å)	∠N−H···F (deg)
		3a (molecule A)		
N1a−H1a···F1a	2.810(4)	1.00(4)	2.21(4)	117(3)
N1a−H1a···F3a	2.819(4)		2.08(4)	128(3)
		3a (molecule B)		
N1b−H1b···F1b	2.883(4)	0.97(3)	2.21(4)	125(3)
N1b−H1b···F3b	2.875(4)		2.18(4)	129(3)
		7a		
N3−H3···F1	2.848(2)	0.82(2)	2.25(2)	130(2)
N3−H3···F3	2.813(2)		2.23(2)	128(2)

appeared in the region where the equatorial hydrogens could be expected. These structures afforded a further indication of weak interactions, which may be qualified as H-bonding. The sum of the van der Waals radii of the fluorine and hydrogen atoms remains in the range of 2.5−2.7 Å, whereas the observed N−H···F short contacts are of 2.08 and 2.23 Å with the NHF angles of 117 and 130° (Table 2). Similarly, a deviation of the NH hydrogen from the plane, defined by the N and two neighboring F atoms, found in the structure of **7a**, is less than 0.16 Å. Moreover, the amino hydrogens in **3a** and **7a** are forced to the axial orientations in consequence of these interactions. In contrast, the reported structures of the related 3-substituted 2,6-diphenylpiperidin-4-ones and 2,4-diphenyl-3-azabicyclo[3.3.1]nonan-4-one show the amino hydrogen at the equatorial position.[18] The axial orientation of the NH hydrogen was also evidenced by the ^{1}H NMR spectra of **3a** and **7a**; particularly **7a** exhibited the benzylic proton signal as a doublet due to the vicinal coupling with the NH proton ($^3J_{CHNH}$ = 12.8 Hz; axial−axial orientation[19]), whereas the benzylic proton resonances in amine **5** and *N*-methyl derivative **7b** were observed as singlets (axial−equatorial interaction). Similarly, the $^3J_{CHNH}$ value of 9.2 Hz for piperidinone **3a** was measured in a C_6D_6 solution.

In contrast to the NMR and X-ray results, the IR spectra did not give an unambiguous evidence of the C−F···H−N interaction, since instead of an expected shift of the NH stretching frequency to lower wavenumbers, due to the intramolecular hydrogen bonding, we observed shifting to a higher frequency for the spectra measured in the solid state as well as in the CCl_4 solution, e.g. the ν(NH) in **5** is of 3297 cm^{-1}, while in **7a** it is of 3444 cm^{-1} (KBr pellet). Similar behavior was also shown by **1** and **3a** [i.e., the ν(NH) values are of 3307 and 3390 cm^{-1}, respectively]. The analogous observation of an increase in ν(CH) frequency, ascribed to the C−H···O three-center hydrogen bond interaction, has been recently reported by Adcock and Zhang.[13] Earlier, Pinchas explained the increase of the aldehydic CH stretching frequency in 2-nitrobenzaldehydes to result from the intramolecular hydrogen bonding.[20]

It is noteworthy that 2-fluorophenyl derivatives **2** and **6**, despite their close geometric relations to compounds **3a** and **7a**, respectively, did not show any indication of the NH···F intramolecular hydrogen bonding. This is probably due to the unfavorable dipole−dipole interactions between the 2-fluorophenyl moieties, which in both cases favor the conformation with the fluorine atoms pointing outward. A through-space coupling of the F atoms to the neighboring methyl groups in the ^{1}H NMR spectra of **2** and **6** ($^6J_{HF}$ is of 1.2 and 3.0 Hz, respectively) may be taken as an evidence of their spatial proximity. Apparently, the above interactions are stronger than the stabilization gained from the hydrogen bonding.

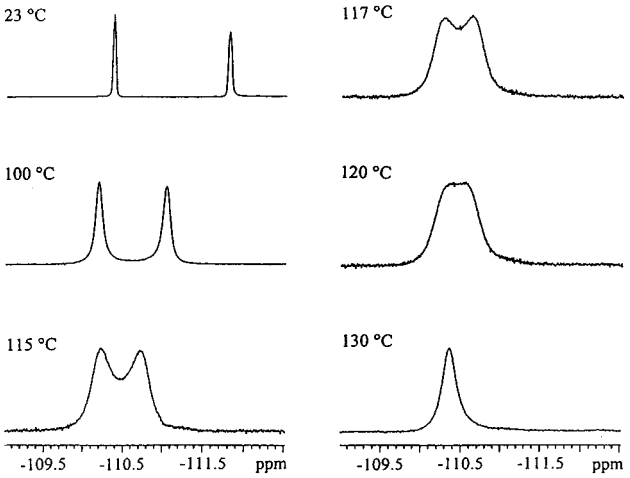

Figure 2. The variable temperature ^{19}F NMR spectra of **7a** in $C_6D_5NO_2$.

Table 3. Free Energies of Activation ($\Delta G^‡$) for the C−C Rotation of the Aryl Groups[a]

compd	solvent	T_C (°C)	$\Delta\nu$ (Hz)	$\Delta G^‡$ (kcal/mol)
3a	$CDCl_3$	47	153	15.1
4	$(CD_3)_2CO$	−76	384	8.7
7a	$C_6D_5NO_2$	119	158	18.6
8	$C_6D_5CD_3$	−43	188	10.6

[a]The errors on $\Delta G^‡$ are of ±0.3 kcal/mol.

Since the rotation of the aryl groups in the 2,6-difluorophenyl derivatives **3a** and **7a** could be possible only after breaking of the NH···F hydrogen bonds, it seems reasonable to estimate the energy of the hydrogen bonding from the C−C rotation barriers of these substituents. The rotation barrier heights found for **3a** and **7** can be compared to those of **4** and **8**, where the fluorines of the 3,5-difluorophenyl moieties are not engaged in the intramolecular H-bonding. Owing to their simplicity, the variable temperature ^{19}F NMR spectra are particularly useful for a determination of the rotation barriers in the fluoroaryl derivatives. On lowering the temperature a decoalescence of the fluorine signals in **8** occurred at −43 °C, whereas coalescence of two fluorine resonances in **7a** was observed at 119 °C (Figure 2). The corresponding free energies of activation $\Delta G^‡$ (Table 3) were calculated by substituting the coalescence temperature (T_c) and the chemical shift difference near the coalescence point ($\Delta\nu$) into the Eyring equation.[21] As it could be expected, the compounds **3a** and **7a** showed higher energy barriers to internal rotation by 6.4 and 8.0 kcal/mol, respectively, than those of **4** and **8**. However, these values are apparently too high to be considered as the energies of the NH···F hydrogen bonds. This is probably due to the fact that besides the hydrogen bond, also the dipole−dipole and steric interactions between the 2,6-difluorophenyl substituents and the NH group in **3a** and **7a** contribute to the rotatory barrier heights. Obviously the

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steric interactions in **3a** and **7a** are stronger than those in **4** and **8**, which may lead to the overestimation of the above values.

Experimental Section

^{1}H, ^{13}C, and ^{19}F NMR spectra were obtained at 500, 50, and 420 MHz, respectively, using a temperature control accessory for variable temperature measurements. The deuterated solvents were used as an internal lock for ^{1}H and ^{13}C NMR. The ^{19}F chemical shifts were referenced to the external $CFCl_3$ standard. Compounds **1**, **5**, **6**, and **7a** were obtained according to the literature methods.[11,12]

t-3,t-5-Dimethyl-r-2,c-6-bis(2-fluorophenyl)piperidin-4-one (2). A solution of ammonium acetate (1.54 g, 20 mmol), 2-fluorobenzaldehyde (4.5 mL, 43 mmol), and 3-pentanone (2.1 mL, 20 mmol) in methanol (15 mL) was refluxed for 4 h. After the reaction mixture was cooled, the precipitated crystals were filtered and recrystallized from toluene−hexane: yield 2.1 g (33%); mp 84−85 °C; ^{1}H NMR ($CDCl_3$) δ 7.68 (m, 2 H), 7.30−7.04 (complex m, 6 H), 4.13 (d, J = 10.6 Hz, 2 H), 2.85 (dq, J = 10.5 and 6.4 Hz, 2 H), 1.77 (br s, 1 H), 0.93 (dd, J = 6.6 and 1.2 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 210.1, 160.5 (d, J_{CF} = 246.5 Hz), 129.1 (d, J_{CF} = 8.7 Hz), 128.6 (d, J_{CF} = 4.1 Hz), 124.6 (d, J_{CF} = 3.4 Hz), 115.4 (d, J_{CF} = 22.8 Hz), 60.5, 51.5, 10.2; ^{19}F NMR ($CDCl_3$) δ −119.1. Anal. Calcd for $C_{19}H_{19}NOF_2$ (315.4): C, 72.36; H, 6.07; N, 4.44. Found: C, 72.10; H, 6.06; N, 4.20.

t-3,t-5-Dimethyl-r-2,c-6-bis(2,6-difluorophenyl)piperidin-4-one (3a) was obtained in a manner similar to that of compound **2** and had mp 119−120 °C (heptane); IR (KBr) 3390, 1713, 1703, 1470 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 2 H), 6.94 (m, 4 H), 4.22 (d, J = 11.3 Hz, 2 H), 3.35 (br s, 1 H), 3.06 (dq, J = 11.2 and 6.7 Hz, 2 H), 0.96 (dd, J = 6.7 and 1.2 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 209.1, 161.0 (br d, J_{CF} = 256 Hz), 129.5 (t, J_{CF} = 10.7 Hz), 116.4 (t, J_{CF} = 17.8 Hz), 111.9 (d, J_{CF} = 23.4 Hz), 58.8, 50.6, 10.7; ^{19}F NMR ($CDCl_3$) δ −113.6, −114.2. Anal. Calcd for $C_{19}H_{17}NOF_4$ (351.3): C, 64.95; H, 4.88; N, 3.99. Found: C, 64.81; H, 4.79; N, 4.05.

1-t-3,t-5-Trimethyl-r-2,c-6-bis(2,6-difluorophenyl)piperidin-4-one (3b). A solution of 33% ethanolic methylamine (1.0 mL), glacial acetic acid (2.0 mL), 2,6-difluorobenzaldehyde (1.1 mL, 10 mmol), and 3-pentanone (0.55 mL, 5 mmol) in ethanol (5 mL) was refluxed for 3 h and left to stand at room-temperature overnight. The precipitated crystals were filtered, washed with methanol, and recrystallized from toluene−hexane: yield 0.36 g (20%); mp 166−167 °C; ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 2 H), 6.89 (m, 4 H), 3.62 (d, J = 11.3 Hz, 2H), 3.42 (m, 2 H), 1.92 (s, 3 H), 0.86 (d, J = 6.6 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 209.4, 161.7 (d, J_{CF} = 250.3 Hz), 161.5 (d, J_{CF} = 250.5 Hz), 129.5 (t, J_{CF} = 10.5 Hz), 112.1 (complex m), 66.4, 46.6, 40.8, 11.1; ^{19}F NMR ($CDCl_3$) δ −109.6, −114.0. Anal. Calcd for $C_{20}H_{21}NOF_4$ (367.4): C, 65.39; H, 5.76; N, 3.81. Found: C, 65.30; H, 5.81; N, 3.62.

t-3,t-5-Dimethyl-r-2,c-6-bis(3,5-difluorophenyl)piperidin-4-one (4) was obtained in a manner similar to that of compound **2** and had mp 137−138 °C (toluene−hexane); ^{1}H NMR ($CDCl_3$) δ 7.01 (dd, J = 8.8 and 2.4 Hz, 4 H), 6.76 (tt, J = 8.7 and 2.0 Hz, 2 H), 3.60 (d, J = 10.2 Hz, 2 H), 2.69 (dq, J = 10.2 and 6.8 Hz, 2 H), 2.12 (br s, 1 H), 0.86 (d, J = 6.8 Hz, 6 H); ^{13}C NMR ($CDCl_3$) 209.0, 163.1 (d, J_{CF} = 249.0 Hz), 162.8 (d, J_{CF} = 249.1 Hz), 145.5 (t, J_{CF} = 8.5 Hz), 110.6 (d, J_{CF} = 24.8 Hz), 103.5 (t, J_{CF} = 25.3 Hz), 67.8, 51.7, 10.3; ^{19}F NMR ($CDCl_3$) δ −106.8 (t, J = 7.2 Hz). Anal. Calcd for $C_{19}H_{17}NOF_4$ (351.3): C, 64.95; H, 4.88; N, 3.99. Found: C, 64.78; H, 4.92; N, 3.92.

1,3,5-Trimethyl-2,4-bis(2,6-difluorophenyl)-3-azabicyclo-[3.3.1]nonan-9-one (7b). Methyl iodide (1.0 mL, 16 mmol) was added to amine **3**[11] (1.89 g, 5 mmol) and potassium carbonate (0.55 g, 4 mmol) in acetone (15 mL) and refluxed for 12 h. After evaporation of the solvent, the residue was taken into benzene, washed with water and aqueous sodium thiosulfate, dried ($MgSO_4$), and evaporated to dryness. The product was crystallized from toluene−hexane: yield 1.4 g (73%); mp 179−180 °C; IR (KBr) 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 2 H), 6.98−6.80 (complex m, 4 H), 3.78 (s, 2H), 3.72 (m, 1 H), 2.12 (m, 2 H), 1.85 (s, 3 H), 1.57−1.37 (complex m, 5 H), 0.87 (d, J = 2.7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 216.3, 161.7 (dd, J_{CF} = 248.8 and 10.2 Hz), 129.4 (t, J_{CF} = 10.7 Hz), 114.9 (t, J_{CF} = 16.7 Hz), 112.5 (d, J_{CF} = 24.3 Hz), 111.4 (d, J_{CF}= 24.1 Hz), 70.9, 51.6, 43.1, 39.2, 20.8, 19.8 (t, J_{CF} = 8.2 Hz); ^{19}F NMR ($CDCl_3$) δ −106.5, −109.2. Anal. Calcd for $C_{23}H_{23}NOF_4$ (405.4): C, 68.14; H, 5.72; N, 3.46. Found: C, 68.12; H, 5.75; N, 3.29.

1,5-Dimethyl-2,4-bis(3,5-difluorophenyl)-3-azabicyclo-[3.3.1]nonan-9-one (8) was obtained in a manner similar to that of compound **2** and had mp 282−283 °C (methanol); ^{1}H NMR ($CDCl_3$) δ 7.08 (dd, J = 8.8 and 2.4 Hz, 4 H), 6.82 (tt, J = 8.7 and 2.4 Hz, 2 H), 3.94 (s, 2 H), 3.25 (m, 1 H), 2.10 (m, 2 H), 1.72 (br s, 1 H), 1.56 (m, 3 H), 0.88 (s, 6 H); ^{19}F NMR ($CDCl_3$) δ −109.9. Anal. Calcd for $C_{22}H_{21}NOF_4$ (391.4): C, 67.51; H, 5.41; N, 3.58. Found: C, 67.78; H, 5.43; N, 3.46.

X-ray Crystal Structure Analysis. Diffraction data were obtained on a Kuma KM-4 diffractometer with graphite monochromated Mo Kα radiation for crystals of **3a** and **7a** with dimensions 0.3 × 0.3 × 0.2 mm and 0.5 × 0.5 × 0.4 mm, respectively. The intensity data for **3a** were collected at 100 K. The structures were solved by direct methods with the program SHELXS-86.[22] Full matrix least-squares refinement was carried out with SHELXL-93[23] on the F^2 values with $F^2 > 0$. The N−H hydrogens for **3a** were localized on ΔF map and refined. Hydrogen atoms bound to C atoms were placed at calculated positions, and their parameters were not refined. In the case of **7a** all hydrogen atoms were localized on ΔF map, and their parameters were included in the refinement.

Crystal data for $C_{19}H_{17}NOF_4$ (**3a**): monoclinic, space group $P2_1/n$, a = 9.561(4) Å, b =16.220(4) Å, c = 21.083(4) Å, β = 90.28(3)°, V = 3270(2) Å^3, Z = 8, D_{calcd} = 1.428 mg m^{-3}, λ(Mo Kα) = 0.71073 Å, T = 100 K, R_1 = 0.0435, wR_2 = 0.1119 for 2980 reflections with $I > 2\sigma(I)$, (R_1 = 0.114, wR_2 = 0.151 for all 4514 data up to $2\theta_{max}$ = 46°), maximum residual electron density is 0.24 e/Å^3.

Crystal data for $C_{22}H_{21}NOF_4$ (**7a**): orthorhombic, space group $P2_12_12_1$, a = 11.580(3) Å, b = 12.598(4) Å, c = 12.699(4) Å, V = 1853(1) Å^3, Z = 4, D_{calcd} = 1.403 mg m^{-3}, λ(Mo Kα) = 0.71073 Å, T = 293 K, R_1 = 0.029, wR_2 = 0.076 for 2887 reflections with $I > 2\sigma(I)$, (R_1 = 0.040, wR_2 = 0.079 for all 3228 data up to $2\theta_{max}$ = 50°), maximum residual electron density is 0.11 e/Å^3.

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Supporting Information Available: The ORTEP drawings, experimental details concerning the crystal structure determination of **3a** and **7a**, atomic coordinates, anisotropic displacement parameters, and lists of bond lengths and angles (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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